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ORIGINAL RESEARCH

Development and Validation of a Dynamic Nomogram for Sepsis-Associated Encephalopathy in Elderly ICU Patients with Sepsis: A Retrospective Cohort Study

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Introduction: The study aimed to develop and validate a nomogram for predicting sepsis-associated encephalopathy (SAE) in elderly patients with sepsis admitted to the intensive care unit (ICU).

Methods: We conducted a retrospective study at the First Affiliated Hospital of Wenzhou Medical University. The least absolute shrinkage and selection operator (LASSO) regression was employed to identify characteristic predictors for SAE, and a nomogram was subsequently developed. The nomogram's performance was evaluated using receiver operating characteristic (ROC) curves, the concordance index (C-index), calibration curves, the Brier score, and decision curve analysis (DCA) to assess discrimination, calibration, and clinical utility. Internal validation was performed using the bootstrap resampling method.

Results: A total of 231 elderly sepsis patients were included in the study, among whom 66 were diagnosed with SAE. The study identified invasive mechanical ventilation (IMV), platelet count, white blood cell (WBC) count, glucose levels, lactate levels, and calcium levels as significant risk factors for SAE. The nomogram demonstrated an area under the curve (AUC) of 0.861, outperforming other predictive factors. The corrected C-index, determined through 500 bootstrap validations, was 0.842. Additionally, the calibration curve indicated strong agreement between predicted outcomes and actual observations. The Brier score of the prediction model was 0.139. Finally, DCA revealed that the nomogram had high clinical applicability.

Conclusion: The prediction nomogram and online website demonstrated strong predictive performance for the occurrence of SAE in elderly patients with sepsis, which made the evaluation process of SAE more convenient and efficient.

Keywords: sepsis-associated encephalopathy, nomogram, sepsis, elderly, intensive care unit, least absolute shrinkage and selection operator

Introduction

SAE is a prevalent complication of sepsis, associated with high mortality rates and significant long-term cognitive and behavioral impairments in survivors.[1,2] These impairments often lead to psychiatric disorders, severely compromising patients' quality of life and imposing substantial economic and social burdens. SAE is diffuse brain dysfunction resulting from a dysregulated host response, irrespective of direct central nervous system infection.[3] The diagnosis of SAE primarily relies on the Glasgow Coma Scale (GCS) or the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[4,5] However, both assessment tools are prone to inter-rater variability, especially when used by untrained personnel. In clinical practice, these diagnostic methods are not only time-consuming and complex but also frequently fail to deliver timely and accurate diagnoses.

With the global aging population, the number of elderly patients admitted to intensive care units has been steadily increasing.[6] SAE is particularly common among elderly patients and predicts poor clinical outcomes. Furthermore, the quality of life of elderly SAE survivors is markedly lower than that of the general population. Much of the previous

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research have demonstrated that the incidence of SAE in elderly patients can exceed 50%,[7,8] and SAE remarkably increases short- and long-term mortality in sepsis patients.[9–11] Therefore, early identification of SAE in elderly patients is crucial and may serve as a valuable tool for clinical management, potentially improving patient prognosis and enhancing post-discharge quality of life.

The objective of this study is to develop a convenient and cost-effective predictive model through retrospective analysis of clinical data to enable the early identification of SAE.

Methods

Patients and Data Collection

The study enrolled 231 participants diagnosed with sepsis between January 2020 and December 2023 at Wenzhou Medical University Affiliated First Hospital in zhejiang Province, China. The inclusion criteria were: (1) patients who were aged 65 years or above; (2) sepsis patients defined by the Third International Consensus Definitions for Sepsis and Septic Shock (sepsis-3).[12] The exclusion criteria were as follows: (1) drug or toxin effects; (2) electrolyte disturbances; (3) metabolic disorders, including diabetic ketoacidosis, hypoglycemia, hepatic encephalopathy, pulmonary encephalopathy, and uremic encephalopathy; (4) primary brain injuries, such as ischemic stroke, hemorrhagic stroke, traumatic brain injury, epilepsy, or intracranial infection; and (5) non-infectious systemic inflammatory reactions, such as burns, severe acute pancreatitis, or trauma. For patients with endotracheal intubation or tracheostomy,the verbal response of the GCS was recorded as "T", with motor response and eye opening scores assessed during routine clinical evaluations. Delirium was screened using CAM-ICU to supplement SAE diagnosis. The study extracted clinical baseline characteristics of patients who fulfilled the inclusion and exclusion criteria.

Laboratory tests included white blood cell, sodium, hematocrit, hemoglobin, platelets, red blood cell distribution width (RDW), blood urea nitrogen (BUN), international normalized ratio (INR), serum creatinine, potassium, glucose, chloride, calcium, and lactate. In addition, the demographic characteristics, vital signs upon admission to the ICU, and sequential organ failure assessment (SOFA) were collected. Additional collected data consisted of hospital length of stay, ICU length of stay, vasoactive drugs (norepinephrine, epinephrine, dopamine, dobutamine, milrinone, vasopressin), hospital mortality, continuous renal replacement therapy (CRRT), and IMV. The diagnostic criteria for SAE in this study were a GCS score of less than 15 or delirium verified by CAM-ICU. Within 24 hours of an ICU admission, we consider the patient's lowest GCS score.

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (No. YS2023571). The ethics committee waived the requirement for informed consent due to the study's retrospective and anonymized nature of this study. All patient identifiers were removed, and dates of birth were replaced with age ranges. Data were stored on a password-protected server accessible only to the research team. This study complied with the Declaration of Helsinki.

The Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement[13] was used as reporting guideline.

Statistical Analysis

The statistical analysis was conducted using R program (version 4.4.1). Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), while categorical variables were presented as percentages. The Chi-square test and the Mann–Whitney *U*-test were used in this study.

Risk factors associated with SAE were identified using LASSO. The lambda=0.050850 for LASSO regression was used to select the best subset of predictors. The multicollinearity of each variable was measured using the variance inflation factor (VIF). The discriminative ability of the nomogram was assessed using the AUC, and the C-index was calculated based on 500 bootstrap samples. Additionally, the AUC values for lactate, white blood cell count, and calcium levels were computed and compared with the nomogram's AUC. Further, a calibration curve using 500 bootstrap samplings and the Brier score was used to evaluate the calibration of the nomogram, while decision curve analysis was employed to assess its clinical utility. Statistical significance was defined as a p-value < 0.05.

Results

Baseline Characteristics of the Study Cohort

We included 231 elderly sepsis patients from Wenzhou Medical University Affiliated First Hospital. Additionally, the patients were divided into two groups (SAE and non-SAE groups) based on whether the patient developed SAE within 24 hours after admission to the ICU. The baseline characteristics between the SAE and non-SAE groups are presented in Table 1. The overall incidence rate of SAE was 28.6%. Among these patients, 60% were male and 40% were female. Patients suffering from SAE had higher SOFA scores and hospital mortality. Furthermore, patients in the SAE group were more likely to require invasive mechanical ventilation, continuous renal replacement therapy, and vasoactive drugs, and had longer hospital stays compared to those in the non-SAE group.

Feature Selection and Nomogram Development

The study employed the LASSO regression to identify risk factors (Figure 1). The optimal value was established to be Lambda=0.050850. The analysis revealed six risk factors for the development of SAE: IMV, platelets, WBC, glucose, lactate, and calcium. Based on these predictive factors, a prognostic nomogram for the occurrence of SAE was subsequently developed (Figure 2). Figure 3 shows a dynamic online nomogram based on the SAE prediction nomogram, available at https://simeng347.shinyapps.io/dynnomapp/.

Table 1 The Baseline Characteristics Between the SAE and Non-SAE Groups

Variables	Total (N = 231)	Non-SAE (N = 165)	SAE (N = 66)	P
Age	75 (70, 81.5)	75 (71, 81)	75.5 (69, 83)	0.427
Gender, n (%)				0.949
Male	139 (60)	100 (61)	39 (59)	
Female	92 (40)	65 (39)	27 (41)	
Temperature (°C)	37.2 (36.8, 38.0)	37.2 (36.9, 38.0)	37.1 (36.7, 37.9)	0.134
HR (beats/min)	104 (88, 119)	101 (86, 118)	109 (93, 122)	0.028
RR (beats/min)	22 (18, 28)	21 (17, 27)	22 (19, 29)	0.206
MBP (mmHg)	81 (71, 92)	82 (71, 92)	80 (72, 93)	0.784
WBC (K/uL)	11.5 (5.1, 17.4)	11.2(4.7, 16.4)	13.0 (5.7, 20.3)	0.179
Hemoglobin (g/L)	100 (76, 125)	100 (77, 124)	101 (74, 127)	0.937
Hematocrit	0.3(0.23, 0.37)	0.3(0.23, 0.37)	0.3(0.22, 0.38)	0.762
RDW (%)	14.1 (13.3, 15.6)	14.1 (13.2, 15.6)	14.2 (13.5, 15.6)	0.272
Platelets (K/uL)	103 (54, 176)	113 (67, 184)	87 (38, 140)	0.008
Glucose (mmol/l)	8.4 (6.5, 11.9)	8.0 (6.4, 10.3)	9.6 (7.0, 15.2)	0.004
BUN (mg/dL)	13 (9.4, 18.6)	12.1 (8.6, 19)	14.6 (11.4, 18.2)	0.065
Serum creatinine (mg/dL)	156 (98, 278)	136 (89, 276)	187 (117, 278)	0.1
Potassium (mEq/L)	3.87 (3.45, 4.34)	3.84 (3.44, 4.33)	3.92 (3.47, 4.37)	0.681
Sodium (mEq/L)	137 (134, 141)	137 (134, 140)	138.5 (135, 142)	0.034
Chloride (mEq/L)	105 (101, 109)	105 (101, 110)	105 (102, 109)	0.957
Calcium (mg/dL)	1.97 (1.8, 2.1)	1.95 (1.8, 2.1)	1.99 (1.8, 2.1)	0.185
Lactate (mEq/L)	3.7 (2.3, 5.7)	3.2 (2.3, 4.9)	5.25 (3.1, 7.1)	< 0.01
INR	1.4 (1.2, 1.6)	1.39 (1.2, 1.6)	1.43 (1.3, 1.7)	0.286
SOFA	7 (4.5, 10)	6 (4, 9)	10 (6, 11.8)	< 0.01
IMV, n (%)	115 (50)	64 (39)	51 (77)	< 0.01
Vasoactive drugs, n (%)	156 (68)	97 (59)	59 (89)	< 0.01
CRRT, n (%)	69 (30)	40 (24)	29 (44)	0.005
Length of hospital (days)	15 (9, 22)	15 (10, 20)	17 (9, 26)	0.323
Length of ICU (days)	6 (3, 12)	5 (3, 10)	8 (5, 17)	0.004
Hospital mortality, n (%)	33 (14)	14 (8)	19 (29)	< 0.01

Note: Vasoactive drugs include norepinephrine, epinephrine, dopamine, dobutamine, milrinone, vasopressin.
Abbreviations: HR, heart rate; RR, respiratory rate; MBP, mean blood pressure; WBC, white blood cell; RDW, red blood cell distribution width; BUN, blood urea nitrogen; INR, international normalized ratio; SOFA, sequential organ failure assessment; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

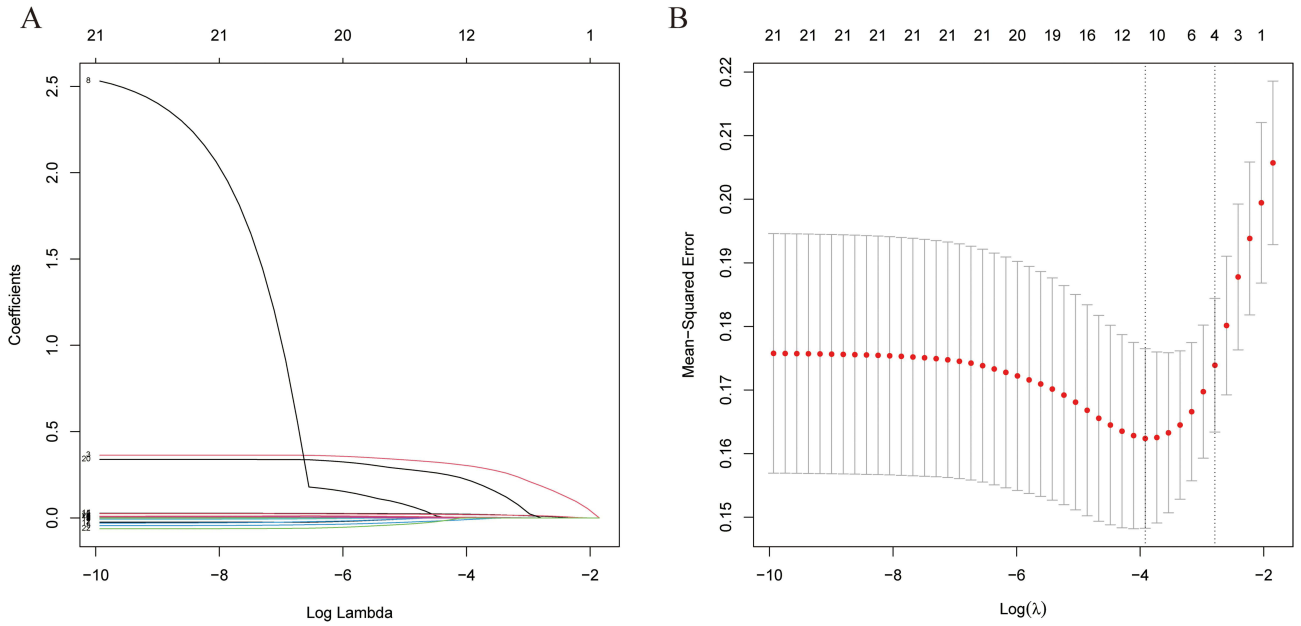

Figure 1 (**A**) LASSO regression coefficient plots for varying penalty parameter values. (**B**) Cross-validation plot for the penalty term.

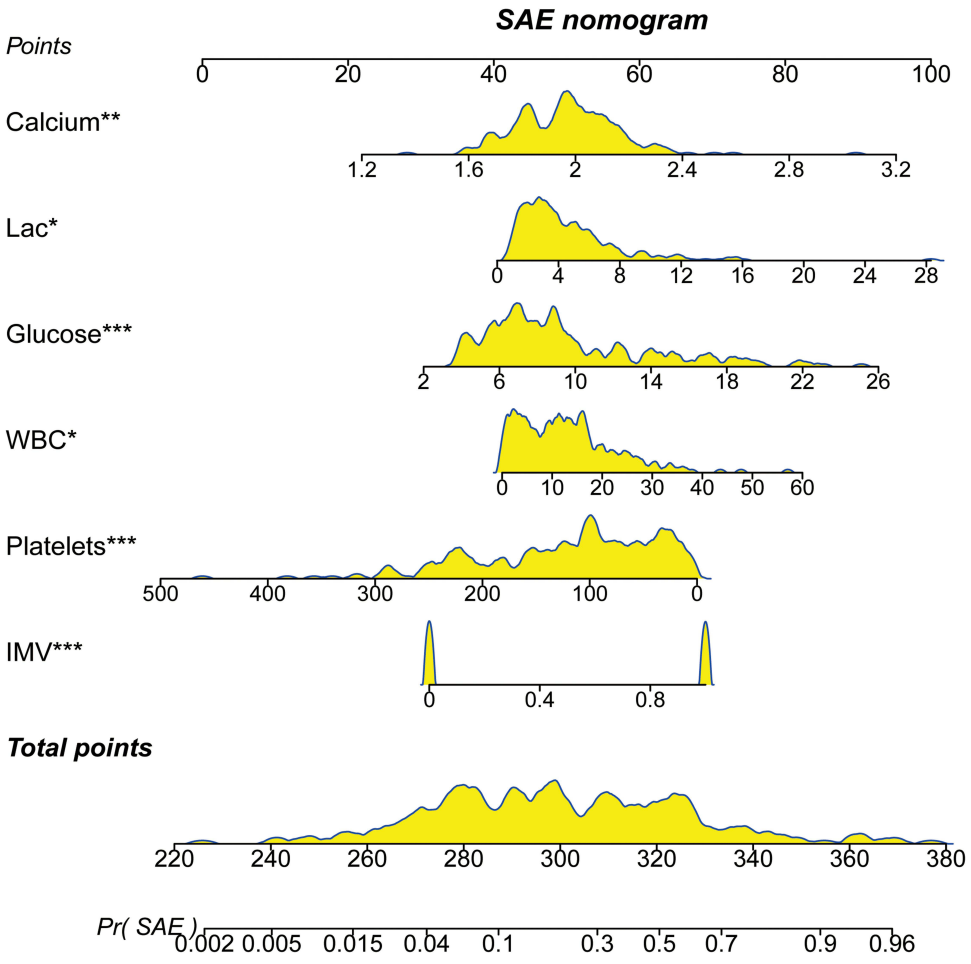

Figure 2 Nomogram predicting SAE probability in elderly sepsis patients. *p < 0.05, **p < 0.01, ***p < 0.001.

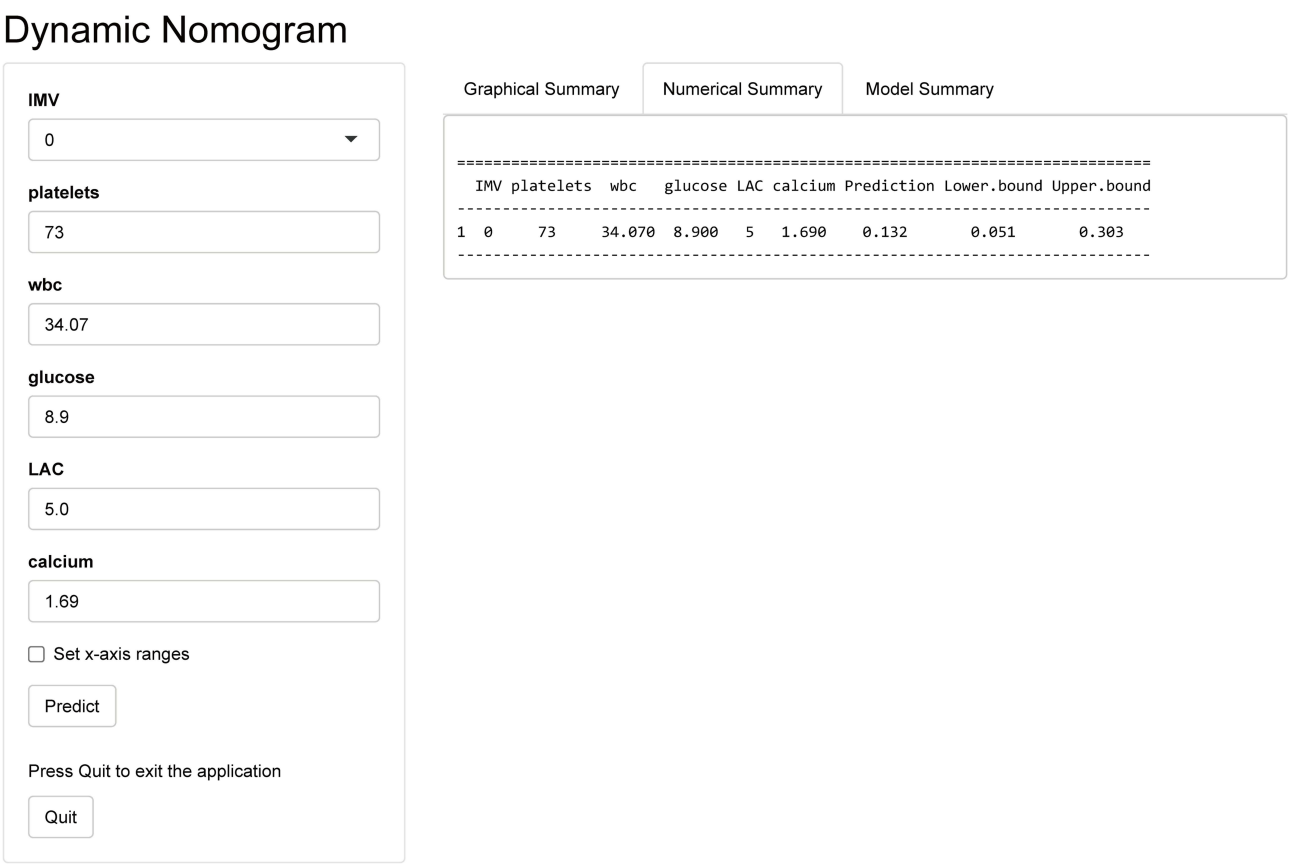

Figure 3 The dynamic online predictive nomogram for SAE. To predict the SAE probability, input variable values and click "Predict" to receive the probability and its 95% confidence interval. For patients on invasive mechanical ventilation (IMV), set IMV=1; otherwise, set IMV=0.
Abbreviations: IMV, Invasive Mechanical Ventilation; WBC, White Blood Cell.

The VIF values of IMV, platelets, WBC, glucose, lactate and calcium were 1.35, 1.27, 1.13, 1.16, 1.04 and 1.18, respectively. The risk factors that were employed in the model all had VIF values below 10, which meant that there was no collinearity between them. The AUC of nomogram was 0.861 (95% CI, 0.814–0.907).The AUC values of lactate, WBC and calcium were also calculated, which were 0.658, 0.557 and 0.556, as illustrated in the Figure 4. The corrected C-index, determined through 500 bootstrapping validations, was 0.842. The Brier score of the prediction model was 0.139.

The nomogram's bootstrap-adjusted calibration curve is shown in Figure 5. The calibration curve demonstrated a strong agreement between the nomogram predictions and the observed data. To demonstrate the clinical applicability of the nomogram, the DCA curve was performed, as illustrated in Figure 6. The nomogram demonstrated a positive net benefit for clinical diagnosis within a threshold probability range of 0.01 to 0.76.

Discussion

This retrospective study aimed to develop a predictive model for the accurate identification of SAE in elderly patients with sepsis. The incidence of SAE in the study cohort was 28.6%. Compared to the non-SAE group, patients with SAE demonstrated significantly higher in-hospital mortality rates and prolonged hospital stays. Utilizing LASSO regression analysis, we identified several independent risk factors for SAE, including white blood cell, platelets, glucose, lactate, use of invasive mechanical ventilation, and calcium. A predictive nomogram for SAE diagnosis was developed based on the findings.

The pathophysiology of SAE is not fully understood. Potential mechanisms may include blood-brain barrier disruption, neuroinflammation and glial cells activation, mitochondria dysfunction and oxidative stress, neurotransmitter

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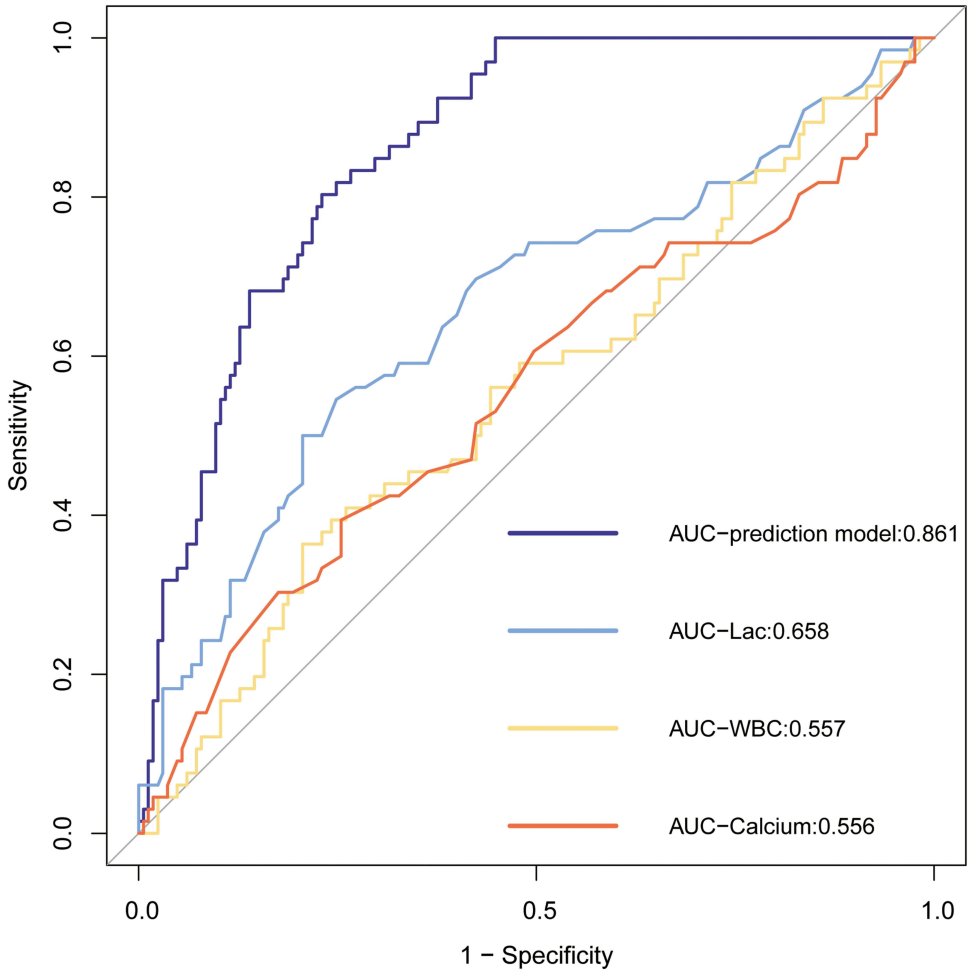

Figure 4 ROC curves for calcium, lactate, WBC, and the nomogram.

alteration, synapse loss, and synaptic plasticity disorder.[14] Blood-brain barrier dysfunction significantly contributes to SAE pathophysiology by exposing the central nervous system to neurotoxic factors like free radicals, inflammatory mediators, intravascular proteins, plasma, and circulating leukocytes.[15] Microglial cells are the brain's primary macrophages and constitute the majority of its immune system. Microglia-mediated neurotoxicity results from cytokines, nitric oxide, excitatory gliotransmitters, and neurotoxic metabolites increasing neuronal excitability, which leads to hyperactivation and excitotoxicity. Astrocytes, the most abundant cells in the brain, are crucial for brain homeostasis, and their dysfunction may contribute to SAE. Mitochondrial dysfunction is proposed to result from electron transport chain inhibition and mitochondrial membrane disruption secondary to severe inflammation.[16] Sepsis-induced cytokines and acetylcholine interaction likely contribute to SAE. Meanwhile, glutamate, γ-aminobutyric acid and 5-Hydroxytryptamine, exhibit alterations in SAE.[17] Dendritic reduction, and synaptic plasticity disorder occur in both acute and chronic neuroinflammation.

In our analysis, lactate levels were significantly elevated in the SAE group. Lactate is commonly considered a glycolysis metabolite produced during hypoxia. Lactate is essential for energy metabolism and signaling in brain tissues, both in normal and pathological conditions.[18] Lactate may increase brain-derived neurotrophic factor levels, enhancing learning, memory, and neuroprotection.[19,20] Meanwhile, elevated serum lactate is a key prognostic biomarker for sepsis.[12,21] Emerging evidence suggests that maintaining lactate levels below 3.5 mmol/L may reduce the incidence of SAE and improve 28-day survival rates in affected patients.[22] Consequently, maintaining normal lactate levels is advisable to reduce the incidence of SAE and mortality in affected patients.

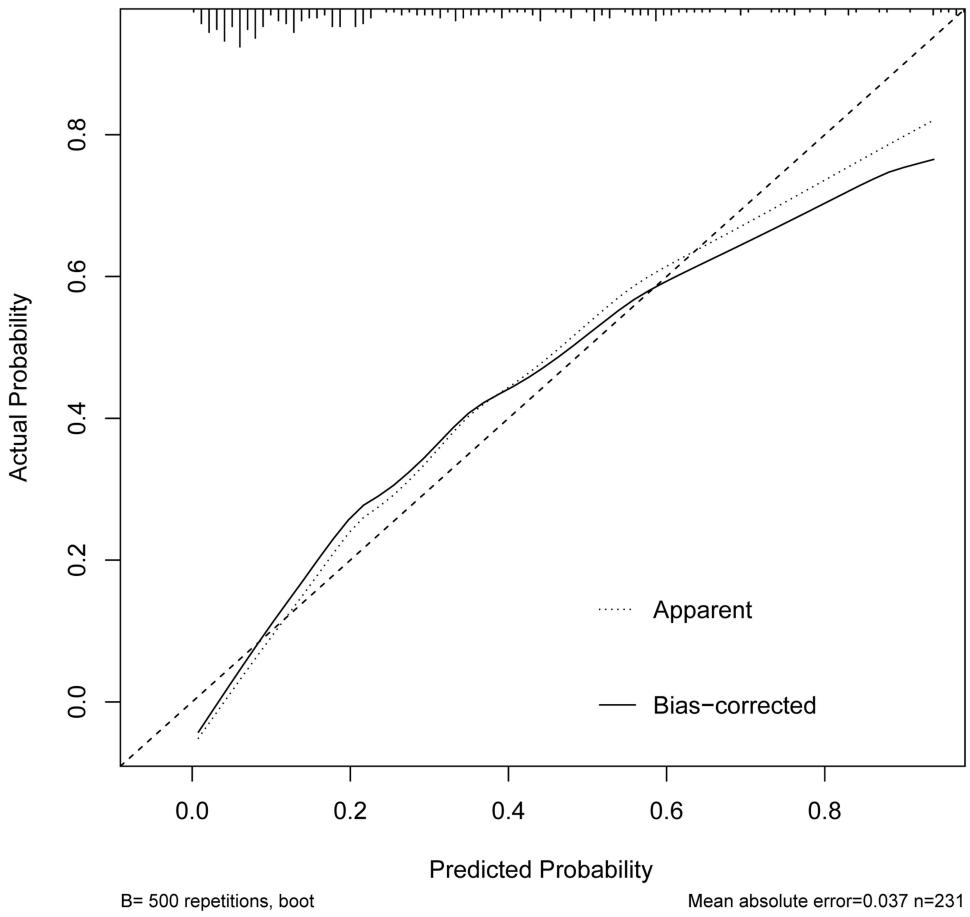

Figure 5 The calibration curve compares the accuracy of original prediction model ("apparent") with bootstrap model ("Bias-corrected") in predicting probability of SAE development, based on 500 repetitions.

Platelets, small, anucleate blood cells derived from bone marrow megakaryocytes, are primarily known for their role in coagulation.[23] However, they are increasingly recognized for their involvement in neurological inflammatory and degenerative diseases.[24,25] In the present study, we found that the SAE group exhibited significantly lower platelet counts ($P<0.05$). Recent evidence has shown that thrombocytopenia is associated with increased mortality in sepsis and septic shock.[26,27] A study which included 16,401 patients with sepsis reported that lower platelet counts were significantly linked to increased 28-day mortality. Platelet count is included in the SOFA score, which evaluates the severity of organ dysfunction in critically ill patients.[28] Thrombocytopenia, which has multifactorial etiologies, is associated with poor prognosis. Consequently, clinicians should actively identify and address the underlying causes.

Blood glucose, a key predictor of SAE, was incorporated into the nomogram in this study. Hyperglycemia is frequently observed in critically ill patients, particularly those with sepsis. Recent data suggests that hyperglycemia may exacerbate inflammation.[29,30] Considering the effect of blood glucose on the mind, this study has excluded diabetes ketoacidosis, hypoglycemia, and hypertonic hyperglycemia. Retrospective analyses showed that hyperglycemia is significantly associated with increased risk of poor outcomes in sepsis.[31–33] The research found that acute hyperglycemia is a distinct risk factor for delirium in critically ill patients, as high glucose levels increase neuroinflammation and delirium by promoting microglial glycolysis and M1 polarization during sepsis.[34] Overall, greater attention should be given to sepsis patients with hyperglycemia, and prompt measures should be implemented to maintain blood glucose levels within an appropriate range.

Recent studies suggest that ultrasonographic measurement of optic nerve sheath diameter (ONSD) may serve as a rapid, non-invasive biomarker for SAE detection.[35] While our current nomogram relies on clinically routine variables, future iterations could integrate ONSD or other dynamic imaging markers to improve real-time SAE monitoring at the

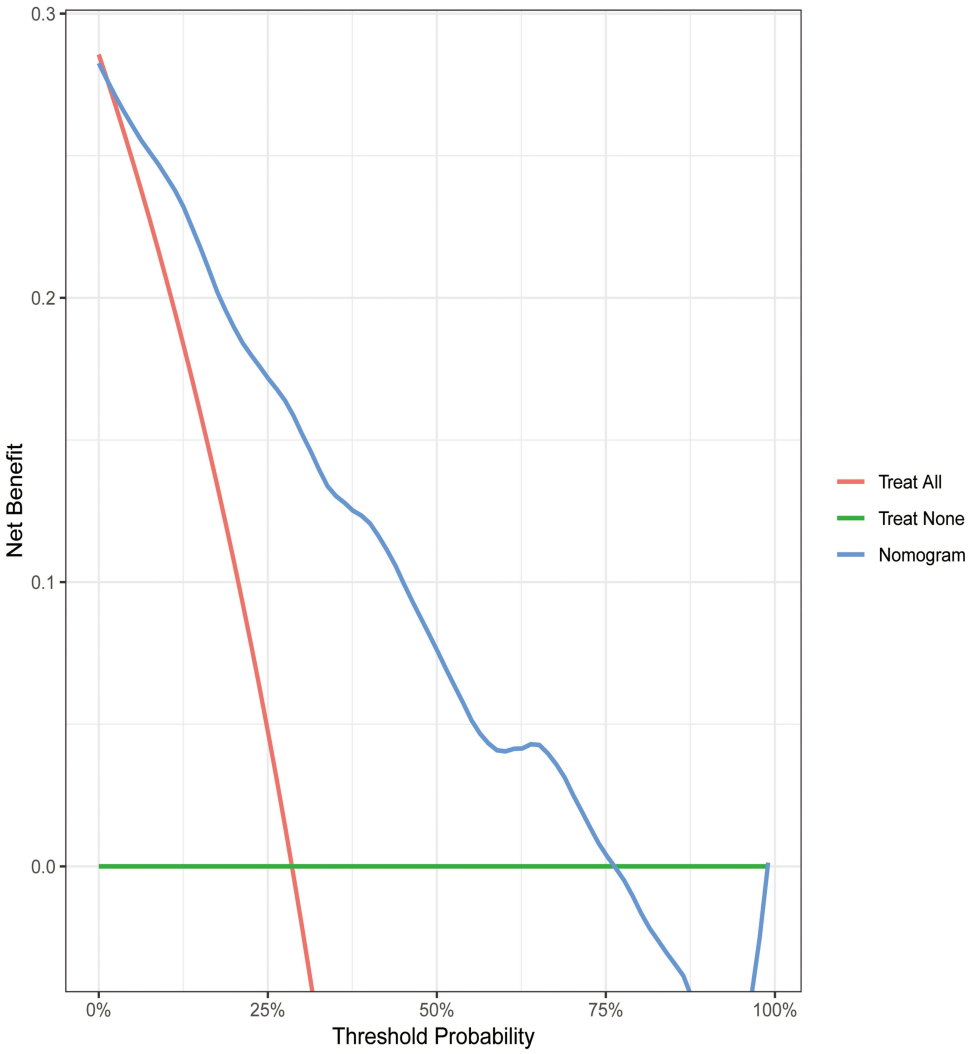

Figure 6 Decision curve analysis of the prediction model for SAE.

bedside. A prior study on adult sepsis patients identified acute renal failure, hypoglycemia, hypercapnia, hypernatremia, and staphylococcus aureus infection as independent predictors of SAE.[36] Independent predictors such as *Staphylococcus aureus* infection are often difficult to identify during the early stages of ICU admission. The independent predictors in our nomogram are easy to collect and low testing cost, aiming to better serve physicians and patients, guiding clinical decision-making and alleviating the burden on healthcare resources. Additionally, the developed nomogram can be integrated into hospital information systems, enabling automatic calculation and display of the risk of SAE, thereby reducing the workload of clinicians.

This study has several limitations. First, this was a single-center study, and the sample size was not particularly large. Consequently, there could unavoidably be a selection bias. Further research with diverse populations and larger cohorts is needed to validate our findings. Second, the nomogram does not incorporate certain biomarkers, such as neurofilament light chains, S100 calcium-binding protein B, and neuron-specific enolase, for predicting the occurrence of SAE due to their clinical inaccessibility and insufficient sensitivity and specificity for accurate SAE prediction.[37–39] Third, we performed only internal validation. Future studies should incorporate external databases to improve model robustness and performance.

Conclusion

A prediction nomogram for SAE was developed and validated, incorporating IMV, platelets, WBC, glucose, lactate, and calcium. This nomogram, along with its online calculator, offers clinicians a visual and personalized tool for early SAE recognition and management, potentially improving prognosis in elderly patients.

Abbreviations

SAE, Sepsis-associated encephalopathy; ICU, Intensive care unit; LASSO, Least absolute shrinkage and selection operator; ROC, Receiver operating characteristic; C-index, Concordance index; DCA, Decision curve analysis; IMV, Invasive mechanical ventilation; WBC, White blood cell; AUC, Area under the curve; GCS, Glasgow Coma Scale; CAM-ICU, Confusion assessment method for the intensive care unit; RDW, Red blood cell distribution width; BUN, Blood urea nitrogen; INR, International normalized ratio; SOFA, sequential organ failure assessment; CRRT, continuous renal replacement therapy; IQR, interquartile range; VIF, variance inflation factor; ONSD, optic nerve sheath diameter.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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